

A Basic Review on Diabetic Neuropathy

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ABSTRACT

Diabetic neuropathy is a major cause of neuropathy worldwide and may lead to amputations and incapacity. This study aimed at a detailed and updated review on diabetic neuropathy, focusing on its epidemiology, classification, clinical features, risk factor, diagnostic investigation and treatment.

KEYWORDS: Diabetic, neuropathy.

INTRODUCTION

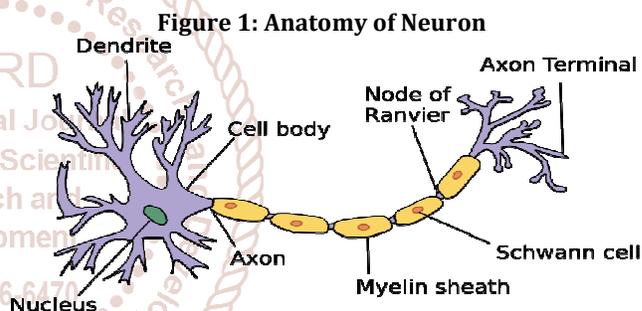
Neuropathy, a common complication of diabetes mellitus, is generally considered to be related to duration and severity of hyperglycaemia. However, it may also occur acutely even with hypoglycaemia. Usually more than 50% of patients with duration of diabetes of 25 years or more are affected, making it as one of the most common disease of the nervous system. One of the largest published series reported a prevalence of 7.5% even at the time of diagnosis of diabetes. The prevalence however, increases progressively without a plateau¹.

Diabetic neuropathy has been defined as presence of symptoms and/or signs of peripheral nerve dysfunction in diabetics after exclusion of other causes, which may range from hereditary, traumatic, compressive, metabolic, toxic, nutritional, infectious, immune mediated, neoplastic, and secondary to other systemic illnesses. Since the manifestations of diabetic neuropathy closely mimic chronic inflammatory demyelinating polyneuropathy, alcoholic neuropathy, and other endocrine neuropathies, hence, before labelling diabetic neuropathy it is mandatory to exclude all other causes of peripheral nerve dysfunction².

Epidemiology:

Diabetes mellitus is a pandemic with a prevalence of 8.3% translating into 371 million diabetics worldwide. It relates to type 2 diabetes mellitus, which may be asymptomatic in many patients for a prolonged duration, and is diagnosed only with the emergence of complications³. Involvement of the nervous system by diabetes was described 150 years ago. With increasing recognition of the variable nature, the classifications of diabetic neuropathy were first suggested in 1893. Almost six decades later, the relationship of neuropathy and duration of diabetes was recognized. Diabetic peripheral neuropathy (DPN) is a well known micro vascular complication of type 2 diabetes mellitus attributed to chronic hyperglycemia, and is defined as the presence of peripheral nerve dysfunction in diabetics after exclusion of other causes⁴. This is associated with further infections, foot ulcers and non traumatic amputations. Estimates of foot infections in type 2 diabetes mellitus range from a lifetime risk of 4 to 7% annually. Neuropathy and neuropathic pain lead to reduced health related quality of life in patients with type 2 diabetes mellitus and impose a huge economic burden on the patients and healthcare system. Apart from the direct costs involved, DPN can also lead to work absence, change in employment and disability⁵. Due to differences in defining and testing diabetic neuropathy, and the type of patient

populations studied, the results of studies on diabetic neuropathy have been variable. Using a combination of clinical symptoms and signs, quantitative sensory testing, nerve conduction studies and heart rate variability, the prevalence was found to be 54% and 45% in type 1 and 2 diabetes respectively in a population based study⁶. Approximately 11.9 million adults in the United States aged > 40 years have diagnosed diabetes. Of those, 3.9 million (32.7%) have diabetic neuropathy and 1.6 million (13.1%) have co morbid neuro and retinopathy.



Classification:

Diabetic neuropathy encompasses a series of different neuropathic syndromes which can be schematized in the following way.

- Focal and multifocal neuropathies:
 - Mononeuropathy
 - Amyotrophy, radiculopathy
 - Multiple lesions "mononeuritis multiplex"
 - Entrapment (e.g. median, ulnar, peroneal)
- Symmetrical neuropathies:
 - Acute sensory
 - Autonomic
 - Distal symmetrical polyneuropathy (DSPN), the diabetic type of which is also known as diabetic peripheral neuropathy (DPN) (most common presentation)⁷.

Pathogenesis:

The following factors are thought to be involved in the development of diabetic neuropathy:

The most distal axons of small fibers distribute in the epidermis of the skin, sensing pain or pricking. Currently, punched skin biopsy immunostained with protein gene product (PGP) -9.5 is widely used for the evaluation of

peripheral neuropathy. The method is simple and minimally invasive, but requires the equipment of confocal laser scan microscopy and skills for the staining and measurement. Usually, skin over the calf muscle is used, but other sites might also be added. In diabetes, the nerve fibers in the epidermis of the skin are significantly affected, resulting in distortion, twisting, focal swelling or beading, and finally, disappearance of nerve fibers. The reduction was found even in subjects of impaired glucose tolerance (IGT) and the extent of fiber loss was marked in established diabetic patients⁸. The nerve fiber loss in the skin was associated with fiber loss in the nerve trunk of the sural nerve, thus in keeping with the presence of clinically evident neuropathy. In relation to the alteration of epidermal innervation, a non-invasive method using corneal confocal microscopy has now been developed for the evaluation of neuropathy. With this method, small nerve fibers distributed in the cornea can be observed without tissue sampling in live conditions. Diabetic patients showed significant loss of nerve fibers, twisting and increased branching on the cornea. Taking advantage of non invasiveness, it is easy to follow by repeated observations and to evaluate the treatment effects on neuropathy by this method. In fact, the recovery of nerve fibers by regeneration was detected in long standing type 1 diabetes mellitus patients 6 months after pancreas transplantation. To understand the cause and the development of neuropathy, spatial and temporal changes of nerve pathology and their clinical significance should be explored in more detail⁹.

Micro vascular disease

Vascular and neural diseases are closely related and intertwined. Blood vessels depend on normal nerve function and nerves depend on adequate blood flow. The first pathological change in the small blood vessels is narrowing of the blood vessels. As the disease progresses, neuronal dysfunction correlates closely with the development of blood vessel abnormalities, such as capillary basement membrane thickening and endothelial hyperplasia, which contribute to diminished oxygen tension and hypoxia. Neuronal ischemia is a well established characteristic of diabetic neuropathy¹⁰. Blood vessel opening agents (e.g. ACE inhibitors, alpha 1 antagonists) can lead to substantial improvements in neuronal blood flow, with corresponding improvements in nerve conduction velocities. Thus, small blood vessel dysfunction occurs early in diabetes, parallels the progression of neural dysfunction, and may be sufficient to support the severity of structural, functional, and clinical changes observed in diabetic neuropathy¹¹.

Sensorimotor polyneuropathy:

Longer nerve fibers are affected to a greater degree than shorter ones because nerve conduction velocity is slowed in proportion to a nerve's length. In this syndrome, decreased sensation and loss of reflexes occurs first in the toes on each foot, then extends upward. It is usually described as a glove stocking distribution of numbness, sensory loss, dysesthesia and night time pain. The pain can feel like burning, pricking sensation, achy or dull. A pins and needles sensation is common. Loss of proprioception, the sense of where a limb is in space, is affected early. These patients cannot feel when they are stepping on a foreign body, like a splinter, or when they are developing a callous from an ill fitting shoe. Consequently, they are at risk of developing ulcer and infections on the feet and legs, which can lead to amputation. Similarly, these patients can get multiple fractures of the

knee, ankle or foot, and develop a charcot joint. Loss of motor function results in dorsiflexion, contractures of the toes, loss of the interosseous muscle function that leads to contraction of the digits, so called hammer toes. These contractures occur not only in the foot but also in the hand where the loss of the musculature makes the hand appear gaunt and skeletal. The loss of muscular function is progressive¹².

Autonomic neuropathy

The autonomic nervous system is composed of nerves serving the lungs, heart, blood vessels, bone, adipose tissue, sweat gland, gastrointestinal system and genitourinary system. Autonomic neuropathy can affect any of these organ systems. The most commonly recognized autonomic dysfunction in diabetics is orthostatic hypotension or becoming dizzy and possibly fainting when standing up due to a sudden drop in blood pressure. In the case of diabetic autonomic neuropathy, it is due to the failure of the heart and arteries to appropriately adjust heart rate and vascular tone to keep blood continually and fully flowing to the brain. This symptom is usually accompanied by a loss of respiratory sinus arrhythmia – the usual change in heart rate seen with normal breathing. These two findings suggest autonomic neuropathy. GI tract manifestations include gastroparesis, bloating, nausea and diarrhoea. Because many diabetics take oral medication for their diabetes, absorption of these medicines is greatly affected by the delayed gastric emptying. This can lead to hyperglycemia when an oral diabetic agent is taken before a meal and does not get absorbed until hours, or sometimes days later when there is normal or low blood sugar already. Sluggish movement of the small intestine can cause bacterial over growth, made worse by the presence of hyperglycemia. This leads to bloating, gas and diarrhoea. Urinary symptoms include urinary frequency, urgency, incontinence and retention. Again, because of the retention of urine, urinary tract infection are frequent. Urinary retention can lead to bladder diverticula, reflux nephropathy and stones¹³.

Clinical Features:

Most symptomatic patients have positive sensory symptoms (excessive response to a stimulus or spontaneously), such as paresthesia and pain, and in some cases may present proprioceptive ataxia. These are referred as sensations of numbness, tingling, imbalance and falls, shocks, pricks and especially burning. They are distributed in LLLl extremities and may evolve to UULL and characteristically patients refer worsening at night. In general these are mild symptoms, however they may be severe and disabling. Negative sensory symptoms (decreased response to a certain stimulus) are those referred as loss of sensitivity in involved segment. At neurologic evaluation there is distal hypoesthesia/hyperesthesia in segments, initially in thermoalgesic sensitivity modalities. In the presence of severe painful neuropathy, there may be hyperesthesia (exaggerated response to tactile stimuli), hyperalgesia (exaggerated sensitivity to painful stimuli), hyperpathia (persistence of pain even after painful stimulus removal) or even allodynia (painful sensation caused by painless stimuli). It may evolve to deep sensitivity hypo/anesthesia such as tactile, vibratory and proprioceptive. In addition, when there is large fibers sensory impairment, there is deep hypo/arreflexia, primarily in Achillean reflex, and there might be global arreflexia in very severe cases¹⁴.

Hyperglycemia:

Hyperglycemia is the other major risk factor of diabetic neuropathy. Its paramount importance has been documented in both type 1 diabetes mellitus and type 2 diabetes. It has been calculated that every 1% increment in HbA_{1c} is connected with approximately 10-15% higher frequency of diabetic neuropathy. Therefore, the effectiveness of strict glycemic control in reducing the incidence and progression of diabetic neuropathy has been the object of several ambitious studies in both types of diabetes. However, an important difference has emerged between type 1 diabetes mellitus and type 2 diabetes mellitus. As detected in a meta-analysis, optimized glycemic control in type 1 diabetes mellitus exerts significantly beneficial effects in preventing the development of clinical diabetic neuropathy and reducing neurological deficits, while in type 2 diabetes mellitus this effect was not (wholly) significant ($p = 0.06$). Another meta-analysis concluded that intensive glucose-lowering treatment was not successful in reducing diabetic neuropathy in patients with type 2 diabetes mellitus. These findings point to a potential difference in terms of the pathogenesis of diabetic neuropathy between the two types of diabetes. However, the data are far from being conclusive, because the trials in type 2 diabetes mellitus have only secondarily looked at diabetic neuropathy, and included only clinical evaluation measures. Therefore, the identification of a beneficial treatment effect was more difficult.

Age:

Age has long been regarded as a risk factor of diabetic neuropathy. Several groups have shown that age exerts an independent effect on diabetic neuropathy, leading to a progressive increase in its prevalence for approximately every decade of life. The independent effect of age has also been shown for prediabetes in epidemiological surveys. However, there is an important caveat in these observations. As age *per se* causes a progressive deterioration in neurological functions, independent of diabetes, the symptoms call for a differentiated interpretation. Delcourt carried out an adjustment for age and found that DSPN no longer correlated with age. On the other hand, it is conceivable that the impact of age on nerve function outweighs the influence of diabetes in the elderly population in which the prevalence of diabetic neuropathy in milder degrees of hyperglycemia (prediabetes) may approach that of known diabetes. Regrettably, no age-adjusted normal values have been used in the vast majority of studies.

Hypertension:

Hypertension is another risk factor for diabetic neuropathy, but there appears to be a difference between the two diabetes types. In type 1 diabetes mellitus, the data is affirmative. Forrest *et al.* have identified hypertension as the strongest predictor of diabetic neuropathy, as it increased the relative risk approximately four times in a 6 year period. Similarly, Tesfaye have reported that systolic hypertension was an independent predictor after adjustment for age, duration of diabetes, and metabolic control. In contrast, studies in type 2 diabetes mellitus have been negative. Of note, tight blood pressure control in the United Kingdom Prospective Diabetes Study did not reduce deterioration of diabetic neuropathy.

Smoking:

There is some evidence that smoking is an independent risk factor of diabetic neuropathy in type 1 diabetes mellitus. In type 2 diabetes mellitus, smoking may also be a risk factor, but its contribution may be weak and not independent. Surprisingly, a protective effect of smoking has been reported in US veterans. More recently, a meta-analysis including 10 prospective and 28 cross sectional studies has found that smoking had an unadjusted OR of 1.26 for prospectively developing diabetic neuropathy (95% CI: 0.86-1.85). In the cross-sectional studies, the pooled OR for diabetic neuropathy due to smoking was 1.42 (95% CI: 1.21-1.65). For both analyses, evidence was graded as low-strength.

Obesity:

In the Southern German population, obesity has been identified as a risk factor of diabetic neuropathy. In the general US and Indian population ≥ 40 years, obesity and the presence of at least 2 cardiovascular risk factors (triglycerides or plasma glucose, reduced HDLc, increased waist circumference, hypertension) increases the likelihood of peripheral neuropathy (OR: 2.20, 95% CI: 1.43-3.39)]. Subjects with morbid obesity have been found to exhibit features of small nerve fiber dysfunction (impaired pain perception and diminished reflex vasodilatation).

Alcohol

Some studies have reported an association between diabetic neuropathy and alcohol consumption, but others have not. In general, it may be difficult to differentiate between diabetic neuropathy with alcohol as a risk factor and alcoholic neuropathy in a person with diabetes. It would be useful to address this differentiation by careful patient selection in a prospective cohort study.

Diagnosis

The diagnosis of diabetic neuropathy can only be made after a careful clinical examination, and all patients with diabetes, should be screened annually for diabetic neuropathy by examining pinprick, temperature, and vibration perception (using a 128-Hz tuning fork), 10 g monofilament pressure sensation at the distal halluces, and ankle reflexes. Combinations of more than one test have 87% sensitivity in detecting diabetic neuropathy. Loss of 10 g monofilament perception and reduced vibration perception predict foot ulcers. Indeed, longitudinal studies have shown that a simple clinical examination is a good predictor of future foot ulcer risk. The feet should be examined for ulcers, calluses, and deformities, and footwear should be inspected. Different scoring systems have been developed for monitoring progression or response to intervention in clinical trials. Other forms of neuropathy, including chronic inflammatory demyelinating polyneuropathy (CIDP), B12 deficiency, hypothyroidism, and uremia, occur more frequently in diabetes and should be ruled out. The practitioner may wish to refer the more complex patient, or those in whom diagnosis needs confirmation, to a neurologist for specialized examination and testing. The diagnosis of chronic diabetic neuropathy is therefore a clinical one and involves the exclusion of nondiabetic causes: investigations should be ordered as dictated by clinical findings and might typically include serum B12, thyroid function, blood urea nitrogen, and serum creatinine. A combination of typical symptomatology and distal sensory loss with absent reflexes,

or the signs in the absence of symptoms, is highly suggestive of diabetic neuropathy¹⁵.

Management:

Many evidences indicate that oxidative stress is involved with diabetes neuropathy genesis. So, antioxidant drugs would be an excellent therapeutic alternative. Intravenous α -lipoic acid (thioctamideMR) (600mg/day for 3 weeks) is currently the only treatment based on disease mechanism with proven efficacy and amenable to be used in the clinical practice⁶⁸. The same drug orally (600mg/ day in fasting), the only presentation currently available in Brazil, still need further evidential studies, although evidences suggest its efficacy. Other treatment modalities were proposed, but still lack data confirming that they are effective¹⁶. Among available drugs for symptomatic pain treatment, there is evidence level A supporting the use of tricyclic antidepressants, anticonvulsants gabapentin and pregabalin, and antidepressant duloxetine, selective dual inhibitor of serotonin and norepinephrine reuptake. There is also second line evidence for the use of opioids such as tramadol and oxycodone. The combination of first line drugs should be considered before using opioids. Tricyclic antidepressants have proven efficacy but their adverse effects are major limiting factors because they might be associated to cardiac conduction changes (A/V blocks, arrhythmias), xerostomy, sweating, dizziness, sedation, urinary retention and glaucoma. Above 100mg/day, their use seems to be associated to sudden death risk, reason why they should be carefully used in cardiopathic patients. It is recommended to start with 10 to 25mg/day and gradually increase the dose with careful follow up of patients. Although doses of up to 150mg/day are indicated, it is hard to go beyond 75mg/day. The choice of the specific drug should take into consideration patients' manifestations and drugs adverse effects.

CONCLUSION:

Besides the fact of many diabetic complications can be reduced with improved blood glucose control and other lifestyle interventions, such as quit smoking and reducing alcohol consumption, the efficacy of these measures, as well as the pharmacological treatments on diabetes neuropathy are not predictable. The medications rated as level A based on their efficacy are able to reduce pain and improve some aspects of patients' quality of life, but are not able to fully eliminate pain or prevent/revert the neuropathy. Even their combination does not result in satisfactory pain control, being the best improvement in pain, restricted to 50% of relief for the majority of the patients. Considering the available pharmacological options, diabetes neuropathy treatment has to be based mainly on patients' symptoms, pain level and tolerance of side effects.

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